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Effect of Intensive Statin Therapy on Coronary High-Intensity Plaques Detected by Noncontrast T1-Weighted Imaging

The AQUAMARINE Pilot Study

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ABSTRACT

BACKGROUND Coronary high-intensity plaques detected by noncontrast T1-weighted imaging may represent plaque instability. High-intensity plaques can be quantitatively assessed by a plaque-to-myocardium signal-intensity ratio (PMR).

OBJECTIVES This pilot, hypothesis-generating study sought to investigate whether intensive statin therapy would lower PMR.

METHODS Prospective serial noncontrast T1-weighted magnetic resonance imaging and computed tomography angiography were performed in 48 patients with coronary artery disease at baseline and after 12 months of intensive pitavastatin treatment with a target low-density lipoprotein cholesterol level <80 mg/dl. The control group consisted of coronary artery disease patients not treated with statins that were matched by propensity scoring (n = 48). The primary endpoint was the 12-month change in PMR. Changes in computed tomography angiography parameters and high-sensitivity C-reactive protein levels were analyzed.

RESULTS In the statin group, 12 months of statin therapy significantly improved low-density lipoprotein cholesterol levels (125 to 70 mg/dl; $p < 0.001$), PMR (1.38 to 1.11, an 18.9% reduction; $p < 0.001$), low-attenuation plaque volume, and the percentage of total atheroma volume on computed tomography. In the control group, the PMR increased significantly (from 1.22 to 1.49, a 19.2% increase; $p < 0.001$). Changes in PMR were correlated with changes in low-density lipoprotein cholesterol ($r = 0.533$; $p < 0.001$), high-sensitivity C-reactive protein ($r = 0.347$; $p < 0.001$), percentage of atheroma volume ($r = 0.477$; $p < 0.001$), and percentage of low-attenuation plaque volume ($r = 0.416$; $p < 0.001$).

CONCLUSIONS Statin treatment significantly reduced the PMR of high-intensity plaques. Noncontrast T1-weighted magnetic resonance imaging could become a useful technique for repeated quantitative assessment of plaque composition. (Attempts at Plaque Vulnerability Quantification with Magnetic Resonance Imaging Using Noncontrast T1-weighted Technique [AQUAMARINE]; UMIN000003567) (J Am Coll Cardiol 2015;66:245–56) © 2015 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

ACS = acute coronary syndrome(s)

CAD = coronary artery disease

CMR = cardiac magnetic resonance

CTA = computed tomography angiography

HbA_{1c} = glycosylated hemoglobin

HDL-C = high-density lipoprotein cholesterol

HIP = high-intensity plaque

hs-CRP = high-sensitivity C-reactive protein

HU = Hounsfield unit

IPH = intraplaque hemorrhage

IVUS = intravascular ultrasound

LAP = low-attenuation plaque

LCL-C = low-density lipoprotein-cholesterol

PCI = percutaneous coronary intervention

PMR = plaque-to-myocardium signal-intensity ratio

RI = remodeling index

TAV = total atheroma volume

T1WI = T1-weighted magnetic resonance imaging

A coronary artery showing high-intensity plaque (HIP) on noncontrast T1-weighted magnetic resonance imaging (T1WI) has been reported to be high risk because of its strong correlation with positive remodeling and low attenuation observed on computed tomography angiography (CTA) or intravascular ultrasound (IVUS) (1). The T1WI technique highlights intraplaque components with short T1 as having a high signal intensity. A necrotic core with intraplaque hemorrhage (IPH) or thrombus gives rise to a short T1 signal (2,3). A plaque-to-myocardium signal-intensity ratio (PMR) ≥1.4 during T1WI may be a significant predictor of major adverse cardiac events in patients with coronary artery disease (CAD) (4). If coronary HIP with a high PMR represents a high-risk plaque and a greater likelihood of unfavorable outcomes, then it is reasonable to propose that a quantitative reduction in HIP may help plaque stabilization.

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Several randomized studies have demonstrated the benefits of statins in reducing both mortality and the incidence of acute coronary syndrome (ACS) (5–7). In addition to reducing levels of serum low-density lipoprotein-cholesterol (LDL-C), statins also may contribute to plaque stability by reducing inflammation (8), improving endothelial function, (9), and reinforcing the fibrous cap (10,11); these effects alter plaque volume and composition, both of which play crucial roles in the progression to ACS (12,13). Serial imaging studies suggest that statins favorably affect the magnitude of the lipid-rich necrotic core (10,14), but there are no prospective studies examining the effect of intensive statin therapy on coronary HIP or IPH. Hence, we undertook the prospectively designed, open-label AQUAMARINE (Attempts at Plaque Vulnerability Quantification with Magnetic Resonance Imaging Using Noncontrast T1-weighted Technique) pilot study to investigate whether intensive statin therapy could decrease the PMR of coronary HIPs through its plaque-stabilizing effects.

METHODS

The AQUAMARINE pilot study was a prospective, open-label, propensity score–matched study at 2 centers examining the effect of 12 months of pitavastatin therapy (with target LDL-C levels <80 mg/dl) on the PMR and CTA measures in patients with CAD. The primary endpoint was the change in the PMR of HIP after intensive pitavastatin treatment. The secondary endpoints were the change in CTA-measured indexes (described below) and high-sensitivity C-reactive protein (hs-CRP) levels as assayed by latex nephelometry from fasting serum samples (SRL, Tokyo, Japan).

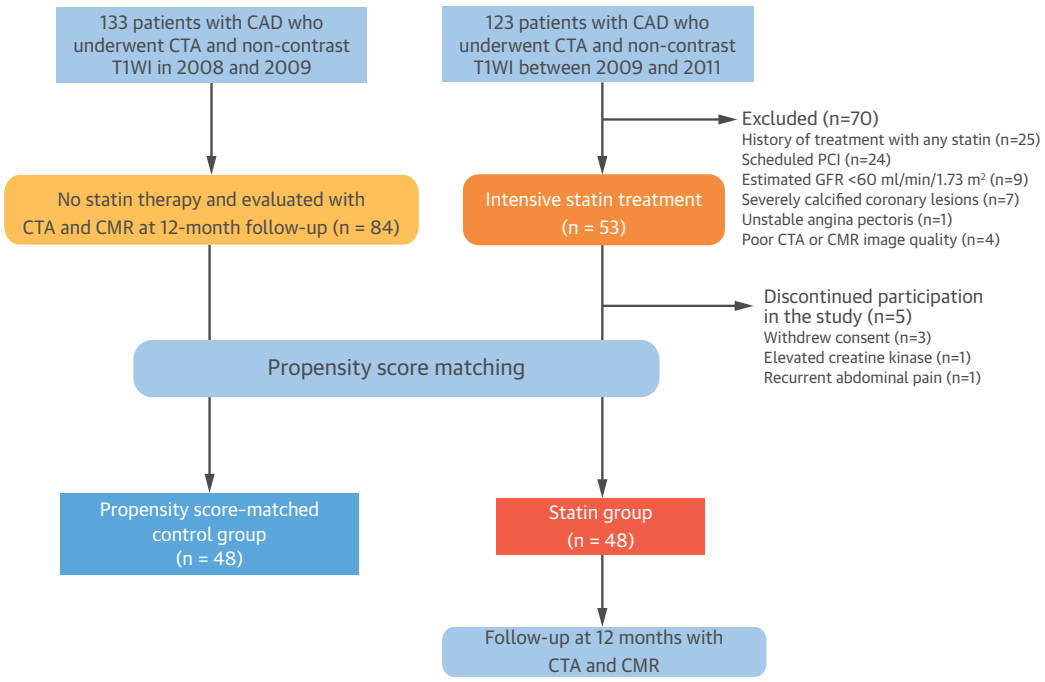
All imaging and laboratory data were analyzed by an independent attending physician and radiologist at the National Cerebral and Cardiovascular Center (Japan), including cardiac magnetic resonance (CMR) and CTA measurements. These evaluators were blinded to patient treatment status. This study was approved by the institutional review board of the National Cerebral and Cardiovascular Center and the ethics committee of Shin-Koga Hospital. Written informed consent was obtained from all enrolled patients.

Between June 2009 and December 2011, 123 consecutive patients with CAD were initially screened with CTA followed by CMR using noncontrast T1WI (**Figure 1**). Patients were excluded if they had 1) a history of treatment with any statin before enrollment (n = 25); 2) scheduled percutaneous coronary intervention (PCI) (n = 24); 3) an estimated glomerular filtration rate <60 ml/min/1.73 m^2 (n = 9); 4) severely calcified coronary lesions detected by CTA (n = 7); 5) unstable angina pectoris (n = 1); or 6) poor CMR or CTA image quality (n = 4). CAD was defined as a history of myocardial infarction or PCI, symptomatic angina pectoris or silent ischemia diagnosed with stress myocardial scintigraphy, or coronary arteriography-verified coronary artery stenosis >25%, as previously reported (4).

In the intensive therapy arm, 53 patients received pitavastatin 4 mg/day to achieve an LDL-C level <80 mg/dl (15). Of these patients, 5 needed to be excluded: 1 patient had elevated creatine kinase levels (although <5 times the upper limit of normal); 1 had recurrent abdominal pain; and 3 patients withdrew consent, leaving 48 patients in the treatment arm (**Figure 1**). CTA and CMR were performed at week 0 (baseline) and at 12 months (follow-up) after pitavastatin administration.

For ethical reasons, the institutional review board did not approve a study in which patients with CAD would be randomized to no lipid-lowering statin therapy. Therefore, the control group consisted of 133 CAD patients who underwent CTA and noncontrast T1WI at baseline and 12 months of follow-up between 2008 and 2009. Of these patients, 84 patients who did not receive statins or other LDL-lowering agents (e.g., ezetimibe) were matched according to a

FIGURE 1 Flow Chart of the Study Patients



This chart depicts the enrollment, exclusion, and matching of patients with coronary artery disease (CAD) who became part of the statin group or the propensity-matched control group. CMR = cardiac magnetic resonance; CTA = computed tomography angiography; GFR = glomerular filtration rate; PCI = percutaneous coronary intervention; T1WI = T1-weighted imaging.

propensity score on the basis of age, sex, body mass index, systolic blood pressure, history of diabetes mellitus, hypertension, dyslipidemia, and current smoking, as well as baseline LDL-C, total cholesterol, high-density lipoprotein cholesterol (HDL-C), triglycerides, glycosylated hemoglobin (HbA_{1c}) levels, hs-CRP, medications, and PMR. Subsequently, 48 propensity score-matched control subjects were included in the study. Control patients not on a statin declined any form of lipid-lowering pharmacotherapy and insisted on dietary intervention alone (n = 39), had a history of an adverse event associated with statin therapy (n = 6), or received ethyl icosapentate (n = 26) or bezafibrate or fenofibrate (n = 13).

CMR IMAGING AND ANALYSIS. CMR imaging consisted of magnetic resonance coronary angiography and plaque T1WI using a commercial 1.5-T magnetic resonance imager (Intera, Philips Medical Systems, Best, the Netherlands). The procedures used to acquire magnetic resonance images in this study have been previously described (4).

The methods that we used to evaluate plaque images also have been described previously (1,4). Briefly, 2 independent experienced investigators who were unaware of the patient data used the T1WI to calculate the PMR at the central core laboratory. The highest signal intensity detected in each plaque was considered the PMR value for that plaque in the segment-based analysis. On patient-based analysis, the highest PMR among the coronary plaques was considered the PMR for that patient. Examination of coronary segments was limited to 1 to 3, 5 to 7, and 11 to 13, on the basis of recommendations from the American Heart Association (16). To confirm that the location of an observed HIP corresponded to the presence of a coronary plaque, we used both cross-sectional and curved multiplanar reformation CTA images. Additionally, we used coregistration images to facilitate confirmation of the anatomic position of high-intensity lesions on T1WI and the coronary vessel on magnetic resonance coronary angiography using commercially available software (Virtual Place Raijin Workstation, AZE, Tokyo, Japan) (4). Regarding PMR quantification of coronary plaques without HIP, when CTA showed >20% coronary stenosis in segments 1 to 3, 5 to 7, or 11 to 13, the PMR of the target

lesion was measured using the coregistration method described previously. The intraobserver intraclass correlation coefficient was 0.94 (95% confidence interval [CI]: 0.80 to 0.98). The interobserver intraclass correlation was 0.88 (95% CI: 0.73 to 0.95). All correlation coefficients for the PMR were >0.8, with narrow CIs, indicating good intraobserver and interobserver agreement (4).

CTA SCANNING AND ANALYSIS. Coronary CTA was performed using a LightSpeed VCT scanner (GE Healthcare, Milwaukee, Wisconsin). The procedures used to acquire CTA images have been previously described (1). We used the same protocol and same dose of contrast medium at both baseline and follow-up CTA in each patient.

We examined coronary segments with >20% diameter stenosis in segments 1 to 3, 5 to 7, and 11 to 13. Quantitative lesion analysis was performed using software that facilitates plaque and lumen volume measurement (Ziostation2, Ziosoft, Tokyo, Japan). Parameters assessed included: 1) plaque volume; 2) remodeling index (RI) with plaques having an RI ≥1.10 considered to be within a positive remodeled artery (17); and 3) Hounsfield unit (HU), as coded by the software into low-attenuation plaques (LAPs) (<30 HU), intermediate attenuation plaques (30 to 150 HU), calcified plaques (351 to 1,000 HU), and lumen (151 to 350 HU) by color. The volume of each component was measured (17,18). Each lesion was analyzed for total atheroma volume (TAV), lumen volume, RI, LAP volume, percentage of total atheroma volume, and percentage of LAP volume.

DATA AND STATISTICAL ANALYSIS. We used propensity-score matching to adjust for the nonrandom absence of statin therapy after CMR and CTA. The propensity score was estimated by using probit regression models (19,20), with pre-evaluation statin administration as the outcome. It included baseline clinical history and presentation characteristics as predictors (covariates are listed in **Table 1**). A propensity score–matched cohort was constructed with statin receivers and nonreceivers matched on a 1:1 basis by a nearest-neighbor matching method within a caliper of 0.05 of the propensity score, using STATA's psmatch2 software (StataCorp LP, College Station, Texas) for propensity-score matching (21). Next, 48 patients were selected for the control group. because we previously identified a PMR of 1.4 as the optimal cutoff value for predicting coronary events (4), both the treatment and control groups were further classified according to the PMR cutoff value of either ≥1.4 or <1.4.

TABLE 1 Baseline Characteristics

	Unmatched Groups			Propensity Score–Matched Groups		
	Statin Group (n = 48)	Control Group (n = 84)	p Value	Statin Group (n = 48)	Control Group (n = 48)	p Value
Age, yrs	62.6	65.0	0.145	62.6	62.7	0.945
Male	44 (92)	71 (85)	0.290	44 (92)	45 (94)	0.782
Hypertension	34 (71)	61 (73)	0.843	34 (71)	35 (73)	0.897
Current smoker	18 (38)	44 (52)	0.107	18 (38)	19 (40)	0.896
Dyslipidemia	40 (83)	48 (57)	0.002	40 (83)	38 (79)	0.712
Diabetes mellitus	30 (63)	42 (50)	0.204	30 (63)	29 (60)	0.806
BMI, kg/m^2	24.8 ± 3.5	24.1 ± 3.0	0.192	24.8 ± 3.5	24.6 ± 2.8	0.815
SBP, mm Hg	143 ± 18	145 ± 22	0.458	143 ± 18	144 ± 20	0.784
TC, mg/dl	208 ± 34	195 ± 31	0.020	208 ± 34	211 ± 38	0.740
LDL, mg/dl	125 ± 25	114 ± 26	0.006	125 ± 25	126 ± 21	0.900
HDL, mg/dl	50 ± 13	51 ± 14	0.754	50 ± 13	51 ± 10	0.748
TG, mg/dl	179 ± 95	155 ± 107	0.190	179 ± 95	167 ± 81	0.592
HbA_{1c}, %	6.1 ± 1.2	6.3 ± 1.7	0.459	6.1 ± 1.2	6.1 ± 1.1	0.902
hs-CRP, mg/l	1.19 (0.65, 3.31)	1.04 (0.43, 2.60)	0.881	1.19 (0.65, 3.31)	1.12 (0.33, 3.42)	0.984
PMR	1.38 (1.20, 1.50)	1.20 (1.03, 1.44)	0.225	1.38 (1.20, 1.50)	1.22 (1.01, 1.56)	0.922
Medications						
Aspirin	43 (90)	74 (88)	1.000	43 (90)	44 (92)	1.000
Beta-blocker	28 (58)	42 (50)	0.372	28 (58)	21 (44)	0.220
ACEI or ARB	21 (44)	35 (42)	0.856	21 (44)	17 (35)	0.532

Values are mean ± SD, n (%), or median (first quartile, third quartile).

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blocker; BMI = body mass index; HbA_{1c} = glycosylated hemoglobin; hs-CRP = high-sensitivity C-reactive protein; HDL = high-density lipoprotein; LDL = low-density lipoprotein; PMR = plaque-to-myocardium signal-intensity ratio; SBP = systolic blood pressure; TC = total cholesterol; TG = triglycerides.

Continuous variables are presented as mean ± SD for normally distributed variables; they were compared using the Student *t* test. Non-normally distributed variables are presented as median (interquartile range). They were compared using a Mann-Whitney *U* test. Categorical baseline variables were compared using the Fisher exact test or the chi-square test as appropriate. Given that plaque lumen volume, TAV, LAP volume, and RI were not normally distributed at baseline, the Wilcoxon signed rank test was used for comparisons involving CTA indexes and PMR between the statin and control groups. Because segments within patients were not independent, predicted PMRs were obtained from a linear mixed model with random intercepts in which each patient was considered as the hierarchy. Two-by-two repeated measures were included in the model with the group (statin vs. control) by time (baseline to follow-up) interaction term adjusted for correlations between individuals and segments. The xtmixed command in STATA was used for modeling.

We used linear regression analysis to assess the relationship between the percentage of change in the PMR during follow-up and the percentage of change in LDL-C, HDL-C, logarithmic hs-CRP, HbA_{1c}, percentage of TAV, and percentage of LAP volume. Statistical significance was defined as $p < 0.05$. All analyses were performed with SPSS for Windows, version 12.0 (SPSS Japan Inc., Tokyo, Japan) and STATA 13 (StataCorp).

RESULTS

Baseline clinical characteristics of the unmatched cohort (Table 1) showed significant differences in the prevalence of dyslipidemia as well as total cholesterol and LDL-C levels. There were 37 HIP-positive (PMR >1.0) patients (77%) in the intensive-statin group, consisting of 17 with a PMR ≥1.4 and 20 with a PMR between 1.0 and 1.4. Among the 48 control patients, 32 (67%) were HIP positive (PMR ≥1.4, n = 11; PMR 1.0 to 1.4, n = 21). As for the matched cohorts, the 2 groups were well matched at baseline, with no statistically significant differences in age, male sex, conventional coronary risk factors, systolic blood pressure, lipid profile, HbA_{1c}, hs-CRP levels, medications used, and PMR between the statin and control groups.

Table 2 shows the comparison of laboratory data at baseline and 12 months (mean: 13.2 ± 0.6; range: 12 to 15 months) in the 48 patients who completed intensive pitavastatin treatment and the 48 propensity score-matched control patients. In the statin group, mean LDL-C decreased from 125 ± 25 mg/dl to 70 ± 11 mg/dl (percentage of change from baseline: −42.1 ± 14.1%; $p < 0.001$), whereas there was no significant reduction in LDL-C in the control patients (from 126 ± 21 mg/dl to 121 ± 25 mg/dl; percentage change from baseline: −3.1 ± 18%; $p = 0.789$). In the statin group, total cholesterol and triglycerides also decreased significantly by the end of follow-up (percentage of change from baseline: −24.8 ± 14.4%; $p < 0.001$; and −22.7 ± 35.8%; $p < 0.001$, respectively). Also, hs-CRP levels were significantly reduced in the statin group (from 1.19 [0.65 to 3.31] mg/l to 0.62 [0.33 to 1.18] mg/l; −46.7 ± 32.2%; $p < 0.001$), but there was no significant change in the control group (from 1.12 [0.33 to 3.42] mg/l to 1.16 [0.48 to 3.58] mg/l; 2.0 ± 21.0%; $p = 0.773$). HbA_{1c} and HDL-C levels did not change significantly during follow-up in either group.

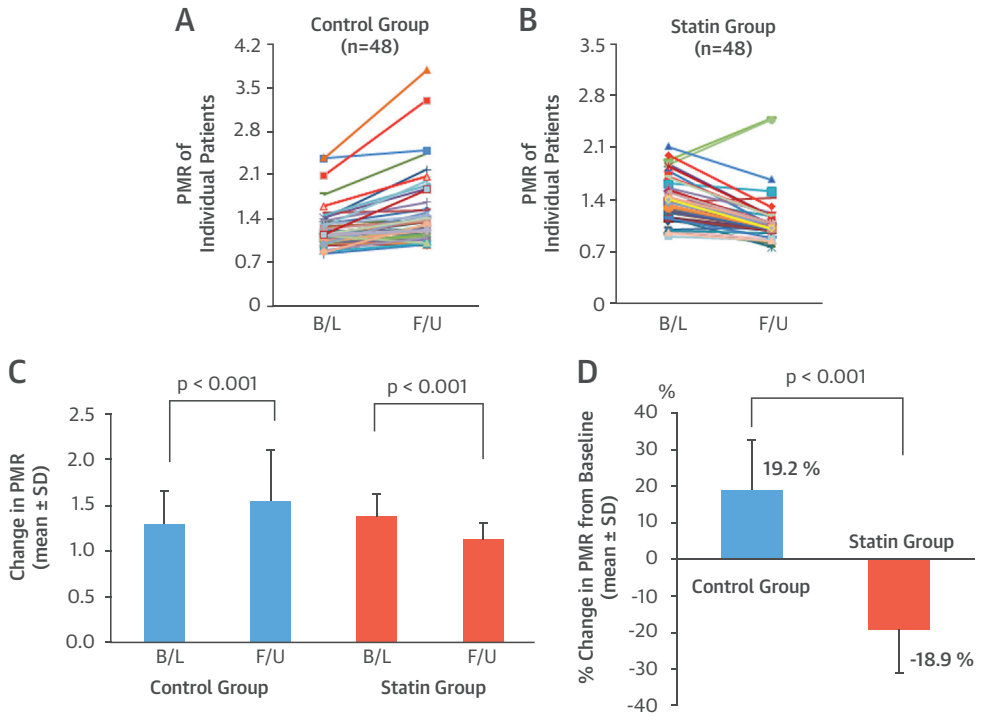
Figure 2 shows the changes in individual-level (Figures 2A and 2B) and group-level data on the PMR (Figures 2C and 2D), the primary efficacy endpoint. The baseline PMR was comparable (statin group: 1.38 [1.20 to 1.50] vs. control group: 1.22 [1.01 to 1.56]; $p = 0.922$). At 12 months, the PMR was significantly lower in the statin group (1.11 [1.02 to 1.25]; 18.9 ± 11.1% reduction from baseline; $p < 0.001$) compared with an increase in the control group (1.49 [1.18 to 1.96];

TABLE 2 Changes in Laboratory Data

	Statin Group			Propensity Score-Matched Control Group			Comparison*		
	Baseline	Follow-Up	p Value	Baseline	Follow-Up	p Value	Statin Group	Control Group	p Value
Lipid profiles									
TC, mg/dl	208 ± 34	152 ± 25	<0.001	211 ± 38	198 ± 34	0.041	−24.8 ± 14.4	−4.8 ± 23	<0.001
LDL, mg/dl	125 ± 25	70 ± 11	<0.001	126 ± 21	121 ± 25	0.789	−42.1 ± 14.1	−3.1 ± 18	<0.001
HDL, mg/dl	50 ± 13	52 ± 13	0.945	51 ± 10	48 ± 11	0.269	4.8 ± 14.0	−5.4 ± 19	0.085
TG, mg/dl	179 ± 95	138 ± 80	<0.001	167 ± 81	158 ± 66	0.244	−22.7 ± 35.8	−5.1 ± 28	0.021
HbA_{1c}, %	6.1 ± 1.2	6.2 ± 1.0	0.828	6.1 ± 1.1	6.2 ± 1.1	0.896	0.6 ± 8.5	1.1 ± 10	0.376
hs-CRP, mg/l	1.19 (0.65–3.31)	0.62 (0.33–1.18)	<0.001	1.12 (0.33–3.42)	1.16 (0.48–3.58)	0.773	−46.7 ± 32.2	2.0 ± 21.0	<0.001

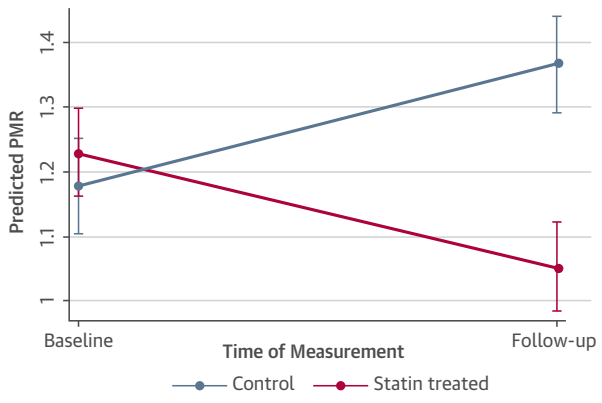
Values are mean ± SD or median (interquartile range). *Percentage of change from baseline over 1 year in the statin versus control group.
Abbreviations as in Table 1.

FIGURE 2 Comparisons of Change in PMR (Patient-Based Analysis)



Individual changes in the plaque-to-myocardium signal-intensity ratio (PMR) from baseline to 12 months in the control **(A)** and statin **(B)** groups. Each line represents 1 patient. **(C)** In the group comparison, there were no significant differences in PMR at baseline, but after 12 months, PMR had increased significantly in the control group and decreased significantly in the statin group. **(D)** A significant net difference was observed in the percentage of change in PMR from baseline between the 2 groups. B/L = baseline; F/U = follow-up.

FIGURE 3 Changes in Predicted PMR



Although baseline plaque-to-myocardium signal-intensity ratio (PMR) values were comparable between the 2 groups, during follow-up, PMR values significantly decreased in the statin group and increased in the control group (each $p < 0.001$).

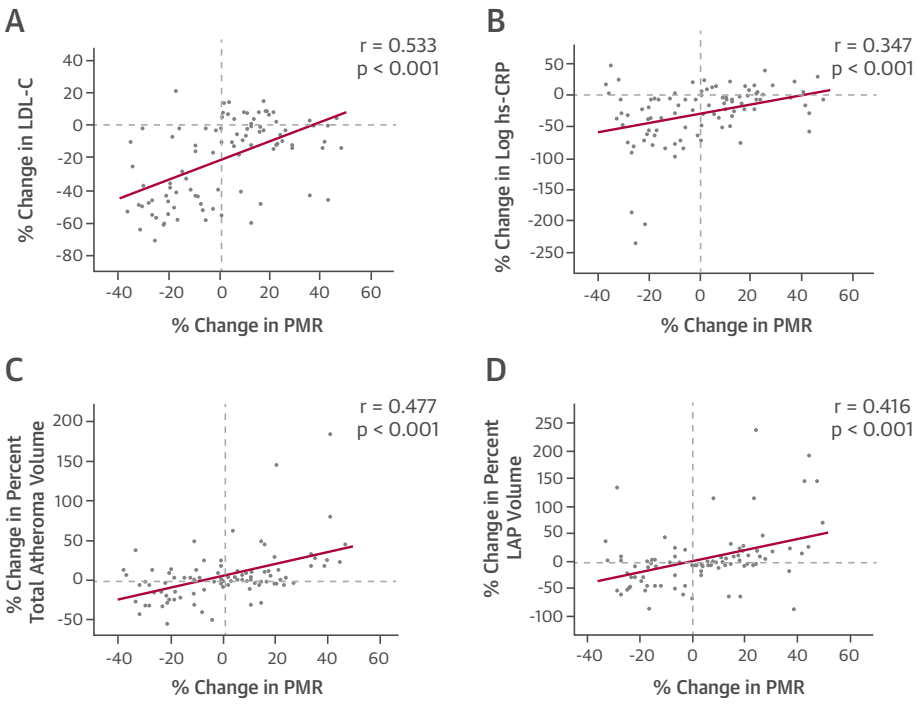
19.2 ± 13.2% elevation from baseline; $p < 0.001$) (Figures 2C and 2D). A significant net difference was observed in the percentage of change in the PMR from baseline between the 2 groups ($p < 0.001$) (Figure 2D). PMRs at baseline and follow-up stratified by statin treatment status and adjusted for individual-level correlations between segments estimated in a linear mixed model are summarized in Figure 3 and Online Table 1. The effect of statin treatment status and the time-by-group interaction term were significant ($p = 0.008$ and $p < 0.001$, respectively). Baseline PMR values were similar in the statin and control groups ($p = 0.241$). During follow-up, PMR values were 0.313 lower in the statin group than in the control group (95% confidence interval: −0.401 to −0.225; $p < 0.001$). PMR values decreased in the statin group but increased in the control group during follow-up ($p < 0.001$). The percentage of change in the PMR was positively correlated with the percentage of change in LDL-C and logarithmic hs-CRP ($r = 0.533$; $p < 0.001$, and $r = 0.347$; $p < 0.001$,

respectively) (Figures 4A and 4B), but not with the percentage of change in HDL-C or HbA_{1c} (data not shown).

SEGMENT-BASED ANALYSIS. We analyzed 768 segments in 96 subjects. In the segment-based CMR analysis, 519 segments were excluded because they either contained lesions scheduled for PCI (18 segments), were previously treated with PCI and stenting (11 segments), had poor imaging quality near stents (48 segments), or had no significant coronary plaques with >20% stenosis identified by CTA (442 segments). The remaining 249 segments were studied and divided into 4 groups according to the cutoff PMR of 1.4 for predicting coronary events on the basis of our previous study (4): statin group/PMR ≥1.4 (25 segments), statin group/PMR <1.4 (111 segments), control group/PMR ≥1.4 (19 segments), and control group/PMR <1.4 (94 segments). Figure 5 shows the changes in the PMR for each segment and summarizes the percentage of change in the PMR from baseline in these 4 groups. In the statin group, the percentage of reduction in the PMR from baseline was greater for PMR ≥1.4 plaques than PMR <1.4 plaques (19.0 ± 12.1% vs. 7.8 ± 11.3%; $p < 0.001$). In the control group, however, the percentage of increase in the PMR from baseline was higher for PMR ≥1.4 plaques (19.7 ± 15.1% vs. 12.0 ± 11.0%; $p = 0.037$).

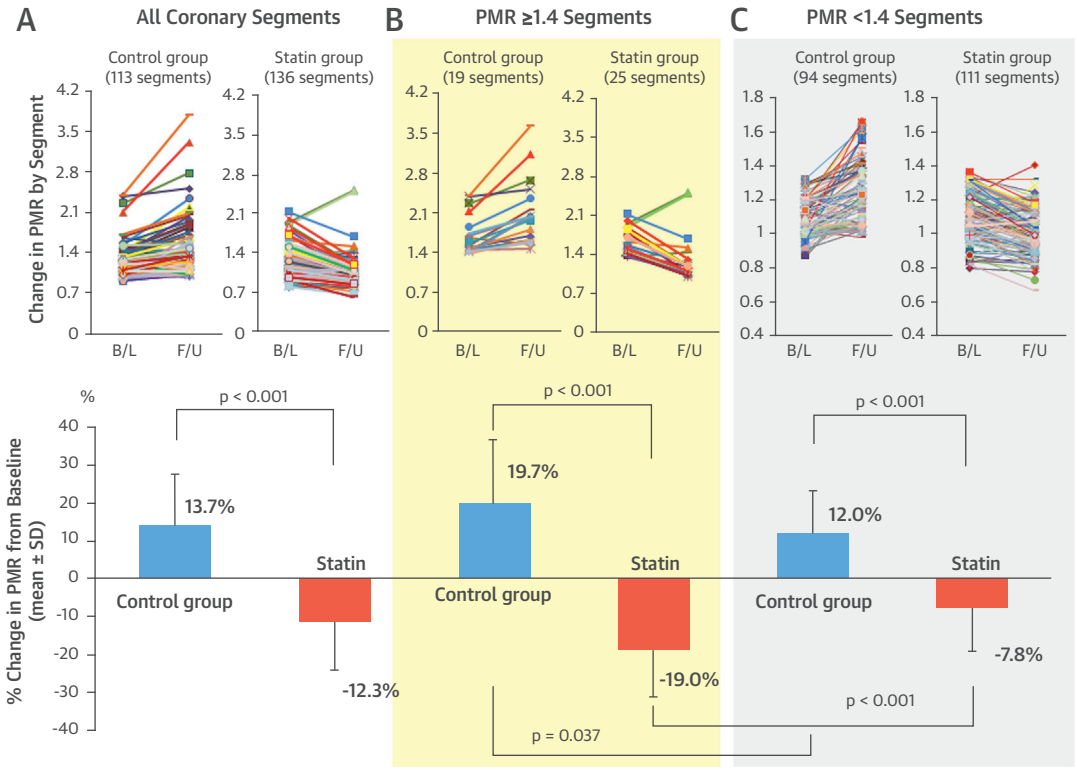
The 249 segments used in the segment-based analysis of change in the PMR were analyzed using CTA (Table 3). In the statin group, significant changes were observed in LAP volume, percentage of TAV, and percentage of LAP volume, whereas TAV, lumen volume, and RI did not significantly change after statin treatment. In the control group, TAV and LAP volume were higher at follow-up but not statistically significant ($p = 0.057$ and $p = 0.091$, respectively); lumen volume, percentage of TAV, percentage of LAP volume, and RI did not change significantly from baseline. Overall, there were significant positive correlations between the percentage of change in the PMR and TAV (Figure 4C) and LAP volume (Figure 4D). Representative CMR and CTA images in the statin and control groups are shown in Figures 6 and 7, respectively.

FIGURE 4 Correlations Between Change in the PMR and Plaque-Related Factors



Significant positive correlations were seen between the percentage of change in the plaque-to-myocardium signal-intensity ratio (PMR) and the percentage of change in low-density lipoprotein cholesterol (LDL-C) **(A)**; logarithmic high-sensitivity C-reactive protein (hs-CRP) **(B)**; percentage of total atheroma volume **(C)**; and percentage of low attenuation plaque (LAP) volume **(D)**.

FIGURE 5 Comparisons of Change in PMR (Segment-Based Analysis)



Individual **(top)** and group **(bottom)** changes in PMR are seen in all coronary segments **(A)**, PMR ≥1.4 segments **(B)**, and PMR <1.4 segments **(C)**. Abbreviations as in Figure 2.

DISCUSSION

The major findings of this pilot study include the following: 1) the PMR of coronary HIP was lowered by statin therapy, which was also associated with decreases in LDL-C and hs-CRP as well as a decrease in the percentage of TAV and percentage of LAP volume as evaluated by CTA; 2) the percentage of change in the PMR was greater in the statin group with PMR ≥1.4 segments; and 3) in the control group, which did not receive statins or other LDL-lowering agents, the PMR was higher at 12 months, especially in patients who had HIP with PMR ≥1.4. The present study suggests the feasibility of using serial CMR examinations using noncontrast T1WI in clinical trials designed to assess changes in coronary plaque characteristics (Central Illustration).

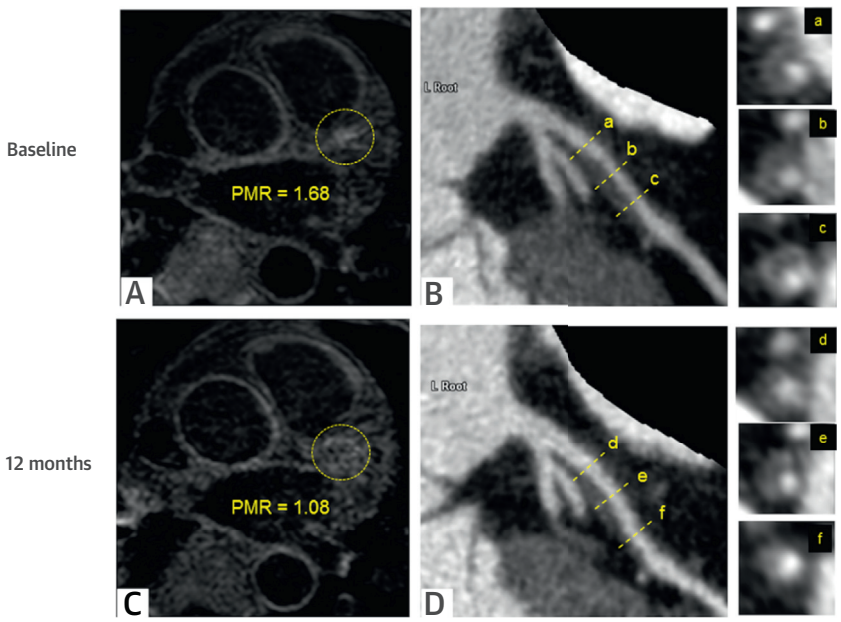
Observations from carotid plaque magnetic resonance imaging and histopathological validation

TABLE 3 CTA Measures

	Statin Group			Propensity Score-Matched Control Group			Comparison*		
	Baseline	Follow-Up	p Value	Baseline	Follow-Up	p Value	Statin Group	Control Group	p Value
TAV, mm^3	195.2 (126.1-255.2)	167.8 (118.2-230.3)	0.078	216.6 (153.9-285.3)	244.1 (144.3-340.6)	0.057	−5.0 ± 26.0	12.4 ± 25.0	0.028
Lumen volume, mm^3	203.9 (135.0-261.8)	201.7 (135.5-265.1)	0.460	197.2 (129.0-296.5)	189.5 (121.8-247.8)	0.095	3.5 ± 21.0	−3.9 ± 13	0.941
LAP volume (<30 HU), mm^3	31.2 (15.2-59.5)	23.3 (10.1-43.8)	0.007	23.7 (15.6-39.6)	25.8 (15.7-45.2)	0.091	−12.8 ± 18.0	8.3 ± 14.2	0.004
Percent TAV	53.6 (39.7-59.4)	46.9 (35.1-59.2)	0.047	55.3 (51.3-60.5)	56.9 (52.5-64.3)	0.381	−4.6 ± 13.6	3.1 ± 11.0	0.108
Percent LAP volume	19.3 (11.3-24.9)	17.0 (8.2-21.1)	<0.001	22.1 (19.3-26.5)	24.5 (19.7-26.1)	0.277	−11.0 ± 23.4	9.9 ± 10.1	<0.001
Remodeling index	1.24 (1.06-1.40)	1.21 (1.14-1.35)	0.145	1.21 (1.11-1.38)	1.23 (1.15-1.41)	0.151	−2.4 ± 9.4	1.7 ± 10.1	0.138

Values are median (interquartile range) or mean ± SD. *Percentage of change from baseline over 1 year in the statin versus control group.
CTA = computed tomography angiography; HU = Hounsfield unit; LAP = low-attenuation plaque; TAV = total atheroma volume.

FIGURE 6 PMR Regression With Statin Treatment



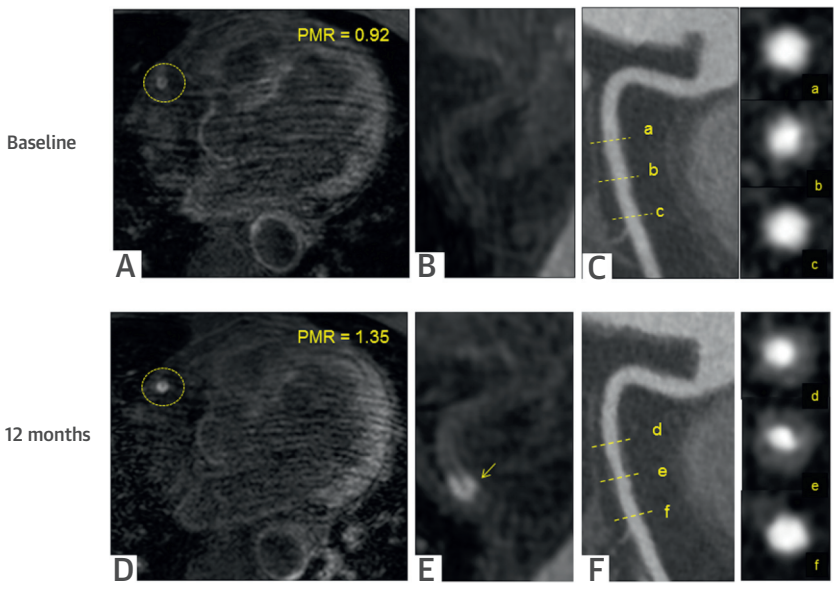
A high-intensity plaque (HIP) with a PMR of 1.68 is observed in the proximal segment of the left anterior descending artery (LAD) at baseline **(A, yellow dotted circle)**. This HIP corresponds to the low-density coronary plaque with positive remodeling in the proximal portion of the LAD on CTA **(B)**. Cross-sectional CTA images of this HIP lesion show positive remodeling with low attenuation plaque (LAP) **(a, b, c)**. After 12 months of intensive statin treatment, PMR decreased to 1.08 **(C, yellow dotted circle)**. CTA at follow-up shows a decrease in LAP volume **(D, d, e, f)**. Abbreviations as in Figures 1 and 2.

studies (2,3,22), as well as studies using optic coherence tomography (23) or specimens obtained through an aspiration catheter during PCI after ACS (24) suggest that a coronary HIP may represent IPH and thrombus formation. Kawasaki et al. (1) systematically evaluated the components of HIPs in patients undergoing CTA and IVUS. Coronary HIPs were closely correlated with IVUS attenuation, as well as with positive vascular remodeling and lower CT density on CTA. The estimation of HIP-PMR provides a useful quantitative measure that can be repeatedly analyzed without the need for radiation exposure, contrast agents, or invasive procedures (1,4). Therefore, it is reasonable to use HIP-PMR for the serial evaluation of plaque characterization, especially in response to plaque-modifying agents.

Numerous carotid magnetic resonance studies have demonstrated the critical role of IPH in plaque instability (25–27) and acute carotid vascular events (28). Statin therapy has been posited to prevent neovascularization (29) and limit the cholesterol content of red blood cell membranes (30) and the phospholipid ratio (31). Carotid IPH was less frequently observed in patients on statins before endarterectomy (32), and the use of statins before a transient ischemic attack or stroke was negatively associated with the presence of IPH (33). On the other hand, statin therapy has been associated with a decrease in the percentage of LAP volume as assessed by CTA (18). Komukai et al. (11) and Hattori et al. (10) demonstrated that stain-induced optical coherence tomography–verified increases in fibrous cap thickness were associated with decreases in serum atherogenic lipoproteins and inflammatory biomarkers. This suggests that statin therapy modifies plaque phenotype including its lipid-rich necrotic core, fibrous cap, and IPH, which in turn might have reduced PMR values in our study. Future studies should investigate whether the effect of statins on HIPs, as monitored by noninvasive CMR, is also associated with reductions in the risk of clinical events.

In our segment-based analysis, the degree of PMR attenuation after statin treatment was significantly greater in the high versus low PMR groups. Conversely, the magnitude of PMR increase was significantly greater in control patients with PMR ≥1.4 segments than control patients with PMR <1.4 segments (Figure 5). Taken together with our previous study demonstrating that coronary lesions with

FIGURE 7 PMR Progression in the Control Group



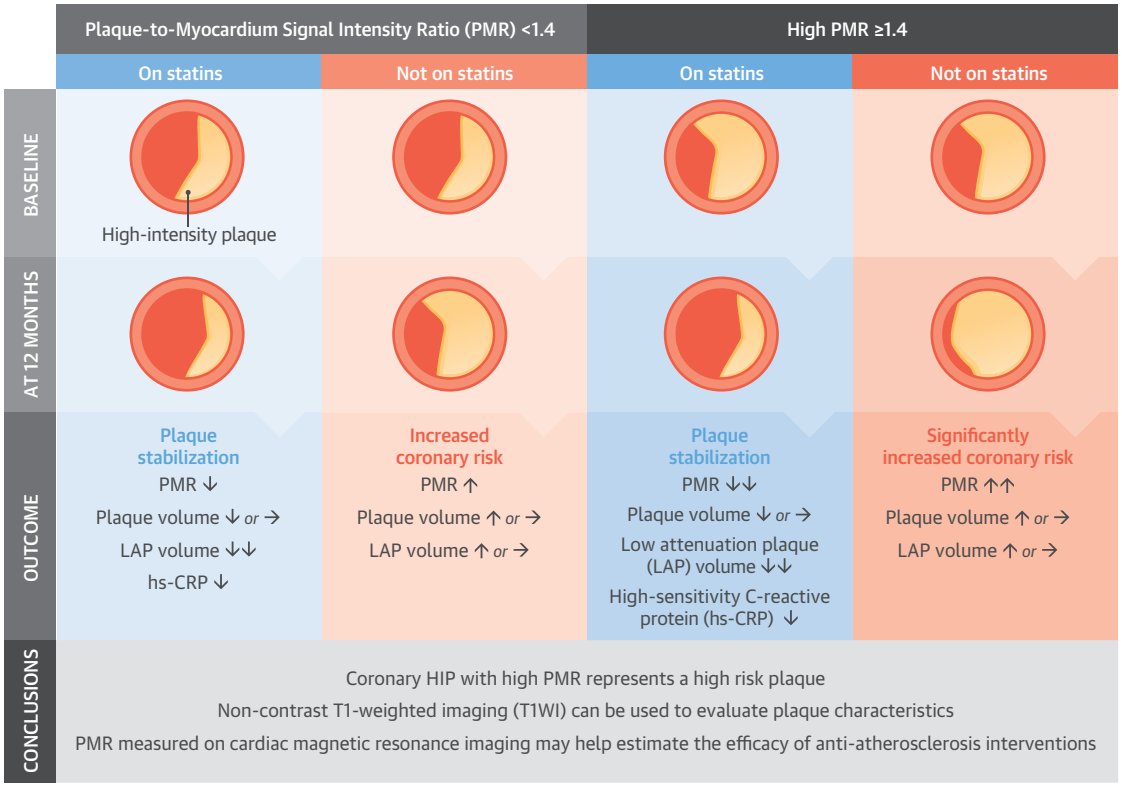
Noncontrast T1-weighted imaging at baseline does not show any HIPs. The PMR was 0.92 in a lesion in the proximal segment of the right coronary artery **(A, yellow dotted circle, and B)**, which corresponds to a minor coronary plaque on CTA **(C, a, b, c)**. However, after 12 months, a representative HIP was observed at the same lesion in the right coronary artery **(D, yellow dotted circle; E, yellow arrow)**, accompanied by an increase in the PMR to 1.35. CTA shows significant progression of coronary plaque morphology **(F, d, e, f)**. Abbreviations as in Figures 2 and 6.

PMR ≥1.4 are at significantly higher risk of subsequent ACS (4), the present findings indicate that coronary lesions with PMR ≥1.4 may be associated with accelerated plaque instability as well as increased signal intensity, which may reflect an increase in the volume of the necrotic core with IPH. This supports recent findings that fateful plaques are usually large with large necrotic cores (34).

However, increases in the PMR were observed even in PMR <1.4 segments (12.0% increase from baseline) (Figure 5), which are considered at lower risk of coronary events on the basis of our previous study (4). This suggests that even HIP with PMR <1.4 might evolve into a high-risk plaque during follow-up. Given that atherosclerosis is a dynamic process, our focus must remain on the entire disease process (35). Early identification of patients with HIP regardless of stenosis severity or plaque burden may prove valuable in the risk stratification of patients with CAD or multiple cardiovascular risk factors, including diabetes mellitus. Additionally, the present study proposes that noncontrast T1WI can potentially be used for comparing plaque characteristics at different time points and may assist in assessing the efficacy of antiatherosclerotic pharmacological interventions.

STUDY LIMITATIONS. As an observational study with a small number of patients examined, there may be inherent flaws related to selection bias, spurious observations, unmeasured covariates, and nonrandom allocation to treatment. However, we sought to minimize these issues by using a propensity model for multivariate analysis and added a summary of coronary events in the 2 groups during follow-up on the basis of an exact logistic regression analysis (Online Table 2). These data suggest that patients with HIPs seem to be at a higher risk of future coronary events. Second, because plaque measurements using CTA were performed semiautomatically, there is a possibility of measurement error. Third, intensive statin therapy did not change TAV and vessel RI as detected by CTA in this study. This was inconsistent with previous IVUS studies demonstrating that intensive statin treatment induces reductions in TAV as well as an absolute decrease in vessel RI (15,36). CTA has lower spatial resolution than IVUS for the measurement of plaque volume, which may in part be related to these inconsistencies. Finally, Noyes et al. (37) reported that plaque regression occurred after an average of 19.7 months of statin treatment. Because target LDL-C levels in this study were comparable with other intensive statin IVUS studies (15,36), mean

CENTRAL ILLUSTRATION **Statin and HIP on CMR**



Noguchi, T. et al. J Am Coll Cardiol. 2015; 66(3):245–56.

Statin therapy reduces the plaque-to-myocardium signal intensity ratio (PMR) of coronary high-intensity plaque (HIP) through its plaque-stabilizing effects in association with decreases in low-density lipoprotein cholesterol, high-sensitivity C-reactive protein (hs-CRP), and low attenuation plaque (LAP) volume. In contrast, the PMR in the control group increased without significant morphological changes detected by computed tomography angiography measures. CMR = cardiac magnetic resonance; IPH = intraplaque hemorrhage; T1WI = T1-weighted imaging.

changes in plaque volume and PMR at 1 year of follow-up were acceptable. However, studies of serial changes in the PMR of HIP beyond 1 year might provide additional insights.

Most importantly, HIP assessment may be more conveniently possible in Japanese subjects by virtue of the body habitus and its applicability elsewhere has yet to be determined. Therefore, the findings and proposals from the study are considered hypothesis generating.

CONCLUSIONS

The present study demonstrates that intensive statin therapy reduces HIP-PMR identified by noncontrast T1WI, which may represent a useful method for quantitatively monitoring changes in plaque vulnerability.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: HIPs detected by noncontrast T1WI are associated with ischemic coronary events.

TRANSLATIONAL OUTLOOK: Further studies are needed to verify the clinical utility of adjusting the intensity of statin therapy based on plaque intensity values assessed by CMR to reduce the risk of coronary events.

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KEY WORDS atherosclerosis, cardiac magnetic resonance, coronary artery disease, vulnerable plaque

APPENDIX For supplemental tables, please see the online version of this article.